RESEARCH PAPER

Cardiovascular Morbidity and Dyslipidaemia Across the Spectrum of Hypothyroidism: A Cross-Sectional Study from a Tertiary Care Centre in Southern India

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Abstract

Background: Thyroid hormone is a principal regulator of myocardial contractility, systemic vascular resistance and lipoprotein metabolism. Whether cardiovascular involvement in hypothyroidism emerges only in overt disease, or is already detectable within the subclinical range, remains incompletely resolved. We assessed the burden of electrocardiographic, echocardiographic and lipid abnormalities across the biochemical spectrum of hypothyroidism.

Methods: This hospital-based cross-sectional study enrolled 100 consecutive adults (aged >18 years) with newly detected biochemical hypothyroidism at a tertiary care teaching hospital in Bengaluru, India, over 18 months. Patients with pre-existing cardiac disease, diabetes mellitus, chronic obstructive pulmonary disease, severe anaemia, other endocrinopathies, or exposure to drugs altering thyroid function were excluded. All participants underwent clinical evaluation, thyroid function testing (chemiluminescence assay), fasting lipid profile, 12-lead electrocardiography and two-dimensional transthoracic echocardiography with Doppler. Left ventricular diastolic function was graded using the Canadian Consensus criteria. Participants were stratified by thyroid status into grade 1 subclinical hypothyroidism (TSH 4.5–10 mIU/L with normal free T4), grade 2 subclinical hypothyroidism (TSH >10 mIU/L with normal free T4) and overt hypothyroidism (elevated TSH with low free T4). Between-group comparisons used Fisher's exact test and Welch's analysis of variance, with the Cochran–Armitage test for trend across ordered strata.

Results: The cohort was predominantly female (81%) with a mean age of 42 ± 15 years; 72 patients had grade 1 subclinical hypothyroidism, 14 had grade 2 subclinical hypothyroidism and 14 had overt hypothyroidism. Electrocardiographic abnormalities were present in 31% overall, most commonly sinus bradycardia (21%), followed by ST–T wave changes (9%) and low-voltage complexes (7%). Echocardiographic abnormalities were identified in 24% of patients: left ventricular diastolic dysfunction in 24% (grade I, 21%; grade II, 3%), increased interventricular septal thickness in 15%, pericardial effusion in 7% and systolic dysfunction in 2%. Every electrocardiographic and echocardiographic abnormality showed a graded increase across thyroid strata: sinus bradycardia rose from 4.2% to 57.1% to 71.4%, and grade I diastolic dysfunction from 2.8% to 57.1% to 78.6% (all $p < 0.001$ for trend). Total cholesterol (168.2 ± 49.4, 204.4 ± 40.8 and 223.1 ± 45.7 mg/dL) and triglycerides (151.2 ± 65.8, 229.6 ± 67.5 and 254.3 ± 72.0 mg/dL) increased significantly across strata (both $p < 0.001$), with a reciprocal decline in HDL cholesterol (37.9 ± 11.8 to 30.1 ± 9.1 mg/dL; $p = 0.033$). Trends for LDL and VLDL cholesterol were directionally concordant but did not reach conventional significance ($p = 0.054$ and $p = 0.057$).

Conclusions: Cardiovascular and lipid abnormalities in hypothyroidism follow a continuous biochemical gradient rather than appearing abruptly at the threshold of overt disease. Clinically silent diastolic dysfunction and atherogenic dyslipidaemia were already detectable in patients with TSH above 10 mIU/L despite normal free T4, supporting a lower threshold for cardiovascular evaluation in this group. Echocardiography and fasting lipid assessment merit consideration in patients with marked TSH elevation even when free T4 is preserved.

Keywords: Hypothyroidism; Subclinical hypothyroidism; Dyslipidaemias; Ventricular dysfunction, left; Echocardiography; Electrocardiography; Thyrotropin

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1. Introduction

Hypothyroidism is among the most prevalent endocrine disorders worldwide, arising from deficient thyroid hormone action at target tissues and producing a generalised deceleration of metabolic processes. In India, community-based data from eight major cities estimate a prevalence of approximately 11%, with a pronounced female predominance and a substantial proportion of cases remaining undiagnosed at the time of survey. Because presenting symptoms are non-specific and often attributed to ageing, anaemia or psychological distress, the diagnosis is frequently delayed until organ-specific consequences have become established.

The heart is a principal target of thyroid hormone. Triiodothyronine regulates transcription of genes encoding sarcoplasmic reticulum calcium ATPase, phospholamban, myosin heavy chain isoforms and β-adrenergic receptors, thereby governing both myocardial contractility and relaxation. Non-genomic actions on membrane ion channels modulate heart rate and conduction, while thyroid hormone-dependent regulation of vascular smooth muscle tone determines systemic vascular resistance. Deficiency of thyroid hormone therefore produces a characteristic haemodynamic profile: bradycardia, reduced cardiac output, impaired ventricular relaxation, elevated systemic vascular resistance and increased arterial stiffness. In parallel, thyroid hormone deficiency reduces hepatic LDL receptor expression and impairs cholesteryl ester transfer and lipoprotein lipase activity, generating an atherogenic lipid phenotype characterised by elevated total and LDL cholesterol.

The clinical consequence of these mechanisms is well established at the severe end of the disease spectrum. Myxoedema heart — with cardiomegaly, low-voltage electrocardiographic complexes, pericardial effusion and impaired contractility — has been recognised for more than a century and is largely reversible with hormone replacement. What remains less settled is the extent of cardiovascular involvement in subclinical hypothyroidism, defined biochemically by an elevated serum thyrotropin with a normal free thyroxine concentration. Meta-analytic data indicate that the excess risk of coronary heart disease events and mortality is concentrated among individuals with TSH concentrations above 10 mIU/L, and international guidance now distinguishes grade 1 (TSH 4.5–10 mIU/L) from grade 2 (TSH >10 mIU/L) subclinical disease on precisely this basis. Whether structural and functional cardiac abnormalities are demonstrable in this intermediate biochemical stratum, and whether they follow a graded relationship with the degree of thyrotropin elevation, has important implications for how aggressively such patients should be investigated and treated.

Indian data addressing this question are relatively sparse, and most published series have dichotomised patients into subclinical and overt categories without resolving severity within the subclinical range. The present study was therefore designed to characterise electrocardiographic, echocardiographic and lipid abnormalities in patients with newly detected hypothyroidism at a tertiary care centre, and specifically to examine whether the burden of these abnormalities varies systematically across three biochemically defined strata spanning mild subclinical to overt disease.

2. Materials and Methods

2.1 Study design, setting and participants

This was a hospital-based, single-centre, observational cross-sectional study conducted in the Department of General Medicine at Sapthagiri Institute of Medical Sciences and Research Centre, Bengaluru, Karnataka, India — a tertiary care teaching hospital serving both urban and peri-urban populations. The study was carried out over an 18-month period from October 2020 to March 2022. Both inpatients and outpatients were eligible. The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from every participant prior to enrolment. The study was conducted in accordance with the Declaration of Helsinki, and the manuscript is reported in accordance with the STROBE statement for cross-sectional studies.

2.2 Sample size

The sample size was estimated using the formula $n = 4pq/d^2$, where p was the prevalence of electrocardiographic changes in hypothyroidism taken as 35.5% from a previously published series, $q = 100 - p$, and d was the permissible absolute error set at 10%. This yielded a minimum requirement of 92 participants, and 100 consecutive eligible patients were enrolled.

2.3 Eligibility criteria

Inclusion criteria

Adults aged more than 18 years with biochemical evidence of hypothyroidism, identified on clinical screening, were eligible for inclusion.

Exclusion criteria

Patients were excluded if they declined consent; had known structural or ischaemic cardiac disease; had chronic obstructive pulmonary disease, severe anaemia, diabetes mellitus or any other endocrine disorder; or were receiving medications known to

alter thyroid function or cardiac rhythm, including beta-blockers, lithium and oral contraceptive preparations. Patients with a history of significant alcohol use were also excluded. These criteria were applied to minimise confounding of both the cardiovascular and lipid endpoints by conditions independently associated with ventricular dysfunction or dyslipidaemia.

2.4 Clinical assessment

All participants underwent a structured history and complete physical examination using a predesigned proforma, including anthropometry, pulse rate, blood pressure and examination of the thyroid gland. Body mass index was calculated as weight in kilograms divided by height in metres squared.

2.5 Laboratory investigations

Venous blood samples (3 mL) were drawn in the early morning after an overnight fast of at least 12 hours. Serum total triiodothyronine, total thyroxine, free thyroxine and thyroid-stimulating hormone were measured by chemiluminescence immunoassay. Fasting lipid profile — total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, very-low-density lipoprotein (VLDL) cholesterol and triglycerides — was estimated by standard enzymatic colorimetric methods on an automated analyser. Lipid abnormalities were interpreted against National Cholesterol Education Program Adult Treatment Panel III thresholds. A complete blood count and other investigations were performed as clinically indicated.

2.6 Electrocardiography

A standard resting 12-lead electrocardiogram was recorded at a paper speed of 25 mm/s and a calibration of 10 mm/mV. Tracings were reported for rate, rhythm, axis, voltage criteria and ST–T segment morphology. Sinus bradycardia was defined as a sinus rhythm with a ventricular rate below 60 beats per minute. Low voltage was defined as a QRS amplitude of less than 5 mm in all limb leads or less than 10 mm in all precordial leads.

2.7 Echocardiography

Two-dimensional transthoracic echocardiography with M-mode, pulsed-wave and continuous-wave Doppler and colour flow mapping was performed using a Philips ultrasound system, with each study interpreted by an operator blinded to the biochemical stratum. Chamber dimensions, interventricular septal thickness and the presence of pericardial effusion were recorded. Interventricular septal thickness was considered increased above 15 mm.

Left ventricular diastolic function was graded according to the Canadian Consensus criteria, which integrate transmitral flow indices (E/A ratio and deceleration time) with pulmonary venous flow parameters (systolic-to-diastolic ratio, atrial reversal velocity and the difference between atrial reversal duration and mitral A-wave duration). A patient was assigned to a grade when at least four of the five criteria for that grade were satisfied.

Left ventricular systolic function was evaluated using systolic time intervals. The pre-ejection period (PEP) was measured as the interval between the onset of the R wave on the electrocardiogram and aortic valve opening, and the left ventricular ejection time (LVET) as the interval between aortic valve opening and closure. The PEP/LVET ratio, which is independent of heart rate and sex, was calculated; a ratio exceeding 0.76 was taken as evidence of systolic dysfunction.

2.8 Definition of thyroid strata

For analysis, participants were stratified into three mutually exclusive strata on the basis of thyroid function: grade 1 subclinical hypothyroidism (TSH 4.5–10 mIU/L with a normal free T4), grade 2 subclinical hypothyroidism (TSH >10 mIU/L with a normal free T4) and overt hypothyroidism (elevated TSH with a low free T4). This stratification follows the grading adopted in contemporary European Thyroid Association guidance, in which a TSH threshold of 10 mIU/L separates mild from severe subclinical disease.

2.9 Statistical analysis

Data were compiled in Microsoft Excel and analysed using SPSS version 22.0 and R version 3.2.2. Continuous variables are summarised as mean ± standard deviation and categorical variables as counts with percentages. Because group sizes were markedly unequal and Levene's test indicated heterogeneity of variance for several lipid parameters, between-group comparison of continuous variables was performed using Welch's analysis of variance rather than the classical F test, with Games–Howell-equivalent pairwise contrasts using Welch's t test and Bonferroni adjustment for three comparisons. Categorical variables were compared using Fisher's exact test, chosen in preference to the chi-square test because several cells contained expected frequencies below five. Because the three thyroid strata are inherently ordered, the Cochran–Armitage test for trend was additionally applied to categorical outcomes and orthogonal polynomial contrasts to continuous outcomes, as these tests have greater statistical power than omnibus tests when a monotonic dose–response relationship is hypothesised. Effect sizes for the comparison of overt disease with grade 1 subclinical disease are reported as Hedges' g. A two-

sided p value below 0.05 was considered statistically significant.

3. Results

3.1 Baseline characteristics

One hundred patients with newly detected biochemical hypothyroidism were enrolled. The mean age was 42 ± 15 years, with the largest number of patients in the fifth decade: 26 patients were aged 41–50 years, 25 were aged 20–30 years and 20 were aged 51–60 years. Only 2 patients were younger than 20 years and 9 were older than 60 years. There was a marked female preponderance, with 81 women and 19 men, corresponding to a female-to-male ratio of 4.3:1. Baseline demographic, anthropometric and clinical characteristics are presented in Table 1.

Mean body mass index was distributed across the normal and overweight ranges: 49 patients were in the 18.5–25 kg/m² band, 33 were overweight (25–30 kg/m²), 6 were obese (>30 kg/m²) and 12 were underweight (<18.5 kg/m²). Thus 39 patients (39%) had a body mass index above the normal range.

Symptoms were dominated by non-specific constitutional complaints. Lethargy was reported by 72 patients, followed by dry skin in 34, menstrual disturbance in 22 of the 81 women, constipation in 17, and cold intolerance and hair loss in 16 each. Cardiovascular symptoms were comparatively infrequent: breathlessness was reported by 9 patients and chest pain by 7, a striking contrast with the 31% prevalence of electrocardiographic abnormality and 24% prevalence of echocardiographic abnormality subsequently documented (Figure 1). On examination, dry skin was present in 34 patients, bradycardia in 21, blood pressure exceeding 130/90 mmHg in 11 and a palpable goitre in 7.

Table 1. Baseline demographic, anthropometric and clinical characteristics of the study population (N = 100).

Characteristic	Category	n (%) or mean ± SD
Age (years)	Mean ± SD	42 ± 15
	< 20	2 (2.0)
	20–30	25 (25.0)
	31–40	18 (18.0)
	41–50	26 (26.0)
	51–60	20 (20.0)
	> 60	9 (9.0)
Sex	Female	81 (81.0)
	Male	19 (19.0)
Body mass index (kg/m²)	< 18.5 (underweight)	12 (12.0)
	18.5–25.0 (normal)	49 (49.0)
	25.0–30.0 (overweight)	33 (33.0)
	> 30.0 (obese)	6 (6.0)
Symptoms	Lethargy / fatigue	72 (72.0)
	Dry skin	34 (34.0)
	Menstrual disturbance*	22 (27.2)
	Constipation	17 (17.0)
	Cold intolerance	16 (16.0)
	Hair loss	16 (16.0)
	Hoarseness of voice	11 (11.0)
	Weight gain	11 (11.0)
	Breathlessness	9 (9.0)
	Chest pain	7 (7.0)
Clinical signs	Body mass index > 25 kg/m²	39 (39.0)
	Dry skin	34 (34.0)
	Bradycardia (< 60 beats/min)	21 (21.0)
	Blood pressure > 130/90 mmHg	11 (11.0)
	Palpable goitre	7 (7.0)

SD, standard deviation. *Denominator is the 81 female participants. Patients could report more than one symptom, so percentages do not sum to 100.

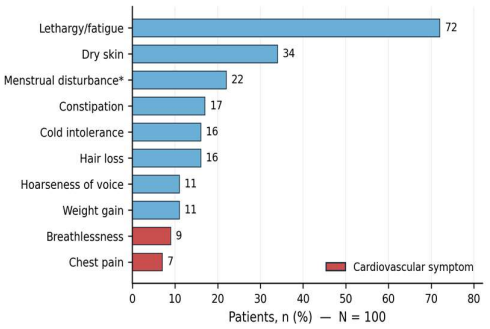

Figure 1. Frequency of presenting symptoms among 100 patients with newly detected hypothyroidism. Cardiovascular symptoms (shaded) were reported by a minority of patients despite objective electrocardiographic abnormality in 31% and echocardiographic abnormality in 24% of the cohort.

3.2 Distribution by thyroid functional status

Stratification by thyroid function assigned 72 patients (72%) to grade 1 subclinical hypothyroidism, 14 (14%) to grade 2 subclinical hypothyroidism and 14 (14%) to overt hypothyroidism (Table 2). Eighty-six per cent of the cohort therefore had biochemically subclinical disease, reflecting the pattern of case detection in a general medical service where thyroid function is frequently tested for non-specific symptoms.

Table 2. Distribution of the study population by thyroid functional status (N = 100).

Stratum	Biochemical definition	n (%)
Grade 1 subclinical	TSH 4.5–10 mIU/L with normal free T4	72 (72.0)
Grade 2 subclinical	TSH > 10 mIU/L with normal free T4	14 (14.0)
Overt	Elevated TSH with low free T4	14 (14.0)
Total		**100 (100.0)**

TSH, thyroid-stimulating hormone; T4, thyroxine. Strata are defined in accordance with European Thyroid Association grading, in which a TSH threshold of 10 mIU/L separates mild from severe subclinical hypothyroidism.

3.3 Electrocardiographic findings

Electrocardiographic abnormalities were present in 31 patients (31%), with the remaining 69 tracings reported as normal. Sinus bradycardia was the single commonest abnormality, documented in 21 patients (21%), followed by ST–T wave changes in 9 (9%) and low-voltage complexes in 7 (7%). Some patients exhibited more than one abnormality.

The distribution of these abnormalities across thyroid strata was strongly graded (Table 3, Figure 2). Sinus bradycardia was present in 3 of 72 patients (4.2%) with grade 1 subclinical hypothyroidism, 8 of 14 (57.1%) with grade 2 subclinical hypothyroidism and 10 of 14 (71.4%) with overt hypothyroidism ($p < 0.001$; $p < 0.001$ for trend). ST–T wave changes and low-voltage complexes were entirely absent in the grade 1 stratum but affected 21.4% and 14.3% respectively of the grade 2 stratum and 42.9% and 35.7% respectively of patients with overt disease (both $p < 0.001$). Notably, all electrocardiographic abnormalities other than bradycardia were confined to patients with a TSH above 10 mIU/L, irrespective of free T4 status.

Table 3. Electrocardiographic abnormalities overall and by thyroid functional stratum.

Finding	Grade 1 SCH (n = 72)	Grade 2 SCH (n = 14)	Overt (n = 14)	Total (N = 100)	p value	p for trend
Normal tracing	69 (95.8)	4 (28.6)	0 (0.0)	69 (69.0)	< 0.001	< 0.001
Sinus bradycardia	3 (4.2)	8 (57.1)	10 (71.4)	21 (21.0)	< 0.001	< 0.001
ST–T wave changes	0 (0.0)	3 (21.4)	6 (42.9)	9 (9.0)	< 0.001	< 0.001
Low-voltage complexes	0 (0.0)	2 (14.3)	5 (35.7)	7 (7.0)	< 0.001	< 0.001

Values are n (%) within each stratum. SCH, subclinical hypothyroidism. p values are from Fisher's exact test across the three strata; p for trend is from the Cochran–Armitage test using ordered scores. Patients could exhibit more than one abnormality, so category counts exceed the number of patients with an abnormal tracing (n = 31).

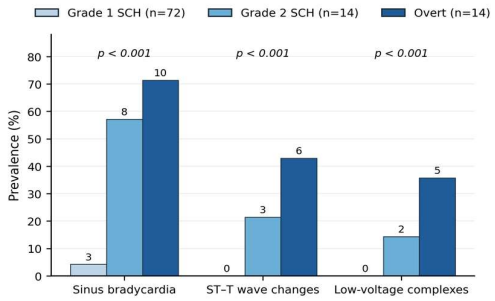

Figure 2. Prevalence of electrocardiographic abnormalities across thyroid functional strata. Bar labels indicate absolute patient numbers. All three abnormalities increased monotonically with biochemical severity; ST–T changes and low-voltage complexes were absent below a TSH of 10 mIU/L. SCH, subclinical hypothyroidism.

3.4 Echocardiographic findings

Echocardiographic abnormalities were identified in 24 patients (24%). Left ventricular diastolic dysfunction was the predominant finding, present in 24 patients (24%), of whom 21 (21%) had grade I and 3 (3%) had grade II dysfunction. Increased interventricular septal thickness was documented in 15 patients (15%), pericardial effusion in 7 (7%) and systolic dysfunction, defined by a PEP/LVET ratio above 0.76, in 2 (2%). All pericardial effusions were

small and haemodynamically insignificant; no patient had evidence of tamponade physiology.

As with the electrocardiographic findings, every echocardiographic abnormality demonstrated a monotonic increase in prevalence across the three thyroid strata (Table 4, Figure 3). Grade I diastolic dysfunction was present in 2.8% of the grade 1 subclinical stratum, 57.1% of the grade 2 subclinical stratum and 78.6% of patients with overt hypothyroidism ($p < 0.001$; $p < 0.001$ for trend). Increased interventricular septal thickness followed the same pattern, rising from 0% to 28.6% to 78.6% ($p < 0.001$), as did pericardial effusion (0%, 14.3% and 35.7%; $p < 0.001$). Grade II diastolic dysfunction (0%, 7.1% and 14.3%; $p = 0.010$) and systolic dysfunction (0%, 0% and 14.3%; $p = 0.002$) were confined almost entirely to the most severe stratum.

The clinical significance of these gradients lies in the grade 2 subclinical stratum. Despite a normal free thyroxine concentration, these 14 patients had a 57.1% prevalence of grade I diastolic dysfunction and a 28.6% prevalence of septal thickening — figures approaching those seen in overt disease and an order of magnitude above the grade 1 stratum.

Table 4. Echocardiographic abnormalities overall and by thyroid functional stratum.

Finding	Grade 1 SCH (n = 72)	Grade 2 SCH (n = 14)	Overt (n = 14)	Total (N = 100)	p value	p for trend
Diastolic dysfunction, grade I	2 (2.8)	8 (57.1)	11 (78.6)	21 (21.0)	< 0.001	< 0.001
Diastolic dysfunction, grade II	0 (0.0)	1 (7.1)	2 (14.3)	3 (3.0)	0.010	0.002
Any diastolic dysfunction	2 (2.8)	9 (64.3)	13 (92.9)	24 (24.0)	< 0.001	< 0.001
Increased IVS thickness	0 (0.0)	4 (28.6)	11 (78.6)	15 (15.0)	< 0.001	< 0.001
Pericardial effusion	0 (0.0)	2 (14.3)	5 (35.7)	7 (7.0)	< 0.001	< 0.001
Systolic dysfunction	0 (0.0)	0 (0.0)	2 (14.3)	2 (2.0)	0.002	0.002

Values are n (%) within each stratum. SCH, subclinical hypothyroidism; IVS, interventricular septum. Diastolic dysfunction was graded by the Canadian Consensus criteria; increased IVS thickness was defined as > 15 mm; systolic dysfunction was defined as a pre-ejection period to left ventricular ejection time ratio > 0.76. p values are from Fisher's exact test; p for trend is from the Cochran–Armitage test.

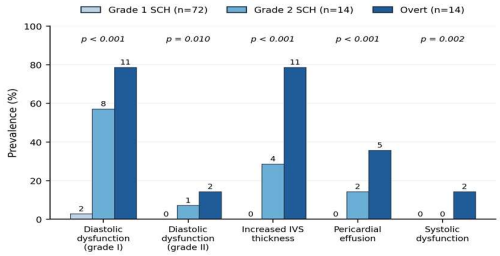

Figure 3. Prevalence of echocardiographic abnormalities across thyroid functional strata. Bar labels indicate absolute patient numbers. Every abnormality increased monotonically with biochemical severity. Note that patients with grade 2 subclinical hypothyroidism — who by definition had a normal free thyroxine — already showed a 57.1% prevalence of grade I diastolic dysfunction. SCH, subclinical hypothyroidism; IVS, interventricular septum.

3.5 Lipid profile

Lipid parameters across the three thyroid strata are presented in Table 5 and Figure 4. Total cholesterol rose progressively from 168.18 ± 49.37 mg/dL in grade 1 subclinical hypothyroidism to 204.43 ± 40.75 mg/dL in grade 2 subclinical hypothyroidism and 223.07 ± 45.69 mg/dL in overt hypothyroidism (Welch's $F = 10.29$, $p < 0.001$; $p < 0.001$ for linear trend). Triglycerides showed the steepest gradient of any parameter measured, increasing from 151.21 ± 65.78 to 229.64 ± 67.54 to 254.31 ± 71.98 mg/dL (Welch's $F = 17.28$, $p < 0.001$), with a large effect size for the comparison of overt disease against grade 1 subclinical disease (Hedges' $g = 1.53$).

HDL cholesterol declined reciprocally across the strata, from 37.93 ± 11.75 mg/dL to 34.57 ± 12.46 mg/dL to 30.07 ± 9.08 mg/dL (Welch's $F = 3.93$, $p = 0.033$; Hedges' $g = -0.68$). LDL cholesterol (98.45 ± 46.37, 106.50 ± 37.99 and 133.14 ± 45.73 mg/dL) and VLDL cholesterol (31.10 ± 23.81, 36.07 ± 11.87 and 42.14 ± 12.58 mg/dL) both increased in the expected direction with moderate effect sizes (Hedges' $g = 0.74$ and 0.49 respectively), but the omnibus comparisons fell marginally short of conventional significance ($p = 0.054$ and $p = 0.057$).

Given the small numbers in the two upper strata, these two parameters are best interpreted as showing a consistent directional signal that the study was underpowered to confirm rather than as evidence of no association.

On pairwise testing with Bonferroni adjustment, patients with overt hypothyroidism had significantly higher total cholesterol (mean difference 54.9 mg/dL, 95% CI 26.6 to 83.2; p = 0.002) and triglycerides (mean difference 103.1 mg/dL, 95% CI 59.4 to 146.8; p < 0.001) and significantly lower HDL cholesterol (mean difference −7.9 mg/dL, 95% CI −13.7 to −2.1; p = 0.030) than patients with grade 1 subclinical hypothyroidism. Differences between the grade 2 subclinical and overt strata did not reach significance for any lipid parameter, consistent with the interpretation that much of the atherogenic shift is already established once TSH exceeds 10 mIU/L.

Table 5. Fasting lipid profile by thyroid functional stratum, with omnibus and trend statistics.

Parameter (mg/dL)	Grade 1 SCH (n = 72)	Grade 2 SCH (n = 14)	Overt (n = 14)	F	p value	p for trend
Total cholesterol	168.18 ± 49.37	204.43 ± 40.75	223.07 ± 45.69	10.29	< 0.001	< 0.001
Triglycerides	151.21 ± 65.78	229.64 ± 67.54	254.31 ± 71.98	17.28	< 0.001	< 0.001
LDL cholesterol	98.45 ± 46.37	106.50 ± 37.99	133.14 ± 45.73	3.29	0.054	0.010
HDL cholesterol	37.93 ± 11.75	34.57 ± 12.46	30.07 ± 9.08	3.93	0.033	0.022
VLDL cholesterol	31.10 ± 23.81	36.07 ± 11.87	42.14 ± 12.58	3.12	0.057	0.080

Values are mean ± standard deviation. SCH, subclinical hypothyroidism; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein. F and p values are from Welch's analysis of variance, used in preference to the classical F test because Levene's test indicated heterogeneity of variance and group sizes were unequal. p for trend is from an orthogonal linear polynomial contrast across the ordered strata. Hedges' g for the comparison of overt hypothyroidism with grade 1 subclinical hypothyroidism was 1.11 for total cholesterol, 1.53 for triglycerides, 0.74 for LDL cholesterol, −0.68 for HDL cholesterol and 0.49 for VLDL cholesterol.

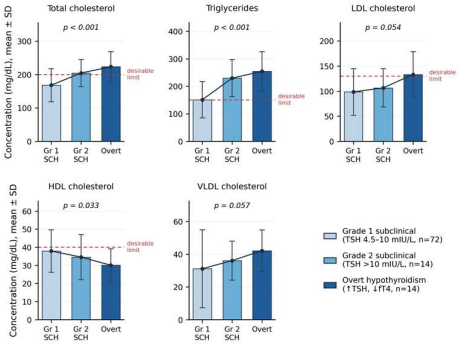

Figure 4. Fasting lipid parameters across thyroid functional strata. Bars show mean values with standard deviation whiskers; the overlaid line traces the group means to illustrate the trend. Dashed red lines mark National Cholesterol Education Program Adult Treatment Panel III desirable thresholds. Total cholesterol and triglycerides rose significantly across strata while HDL cholesterol fell; LDL and VLDL cholesterol showed concordant directional trends that did not reach conventional significance.

4. Discussion

In this cross-sectional study of 100 adults with newly detected hypothyroidism, cardiovascular and lipid abnormalities were common, largely subclinical, and distributed along a continuous gradient of biochemical severity. Nearly a third of patients had an abnormal electrocardiogram and a quarter had an abnormal echocardiogram, yet fewer than one in ten reported breathlessness and fewer than one in fourteen reported chest pain. This dissociation between symptom burden and objective cardiac involvement is the central clinical observation of the study and argues that reliance on cardiovascular symptoms to select hypothyroid patients for further evaluation will systematically miss disease.

The demographic profile of our cohort is consistent with the Indian literature. The mean age of 42 ± 15 years is comparable to the 46 ± 14 years reported by Unnikrishnan and colleagues in their multicity epidemiological survey, and the 81% female preponderance closely matches the 76% reported by Lakshetty and Devru in a North Karnataka series. The predominance of non-specific symptoms — lethargy in 72% and dry skin in 34% — likewise mirrors previous descriptions and reinforces the low specificity of the clinical syndrome.

Sinus bradycardia was the commonest electrocardiographic abnormality at 21%, in keeping with the 30% reported by Lakshetty and Devru and

with the pathophysiology of reduced sinoatrial node automaticity resulting from diminished thyroid hormone-dependent expression of hyperpolarisation-activated cyclic nucleotide-gated channels. Low-voltage complexes occurred in 7% of our cohort, a lower figure than the 24% reported in the same North Karnataka series, plausibly reflecting the smaller proportion of patients with overt disease in our study — only 14% — since low voltage is largely attributable to pericardial effusion and myxoedematous infiltration, both features of advanced disease. Our overall pattern accords with the graded relationship reported by Chandregowda, in whom bradycardia rose from 6.3% in mild to 14.3% in moderate and 40% in severe hypothyroidism.

Diastolic dysfunction was the dominant echocardiographic abnormality, affecting 24% of our patients — closely comparable to the 20% reported independently by Saxena and colleagues and by Shrivastava and Tiwari. Impaired ventricular relaxation is the earliest and most sensitive cardiac manifestation of thyroid hormone deficiency, arising from reduced transcription of sarcoplasmic reticulum calcium ATPase and relative overexpression of its inhibitor phospholamban, which together slow diastolic calcium reuptake. Increased interventricular septal thickness in 15% of our cohort is close to the 16% reported by Shrivastava and Tiwari and probably reflects a combination of myxoedematous interstitial deposition of glycosaminoglycans and the pressure load imposed by elevated systemic vascular resistance. Pericardial effusion occurred in 7%, lower than the 13% reported by Kumar and colleagues and considerably below the 30–80% historically described in frank myxoedema, again consistent with the modest representation of overt disease in our sample.

Systolic dysfunction was rare, affecting only 2 patients, both with overt hypothyroidism. This is congruent with the observation of Rawat and Satyal, who found no systolic impairment in a younger hypothyroid cohort, and with the general principle that diastolic abnormalities precede systolic ones in thyroid heart disease. It is worth noting, however, that conventional systolic indices may be insensitive: Tafarshiku and colleagues, using tissue Doppler and strain imaging, demonstrated impaired longitudinal systolic function in hypothyroid patients whose conventional ejection indices were preserved, suggesting subendocardial dysfunction that our systolic time-interval methodology would not have detected.

The lipid findings reproduce the classical hypothyroid dyslipidaemia and extend it across severity strata. Total cholesterol and triglycerides increased significantly with worsening thyroid status while HDL cholesterol fell, a pattern mechanistically attributable to downregulation of hepatic LDL receptor expression, reduced lipoprotein lipase and hepatic lipase activity, and impaired reverse cholesterol transport. Our total cholesterol values across strata (168.2, 204.4 and 223.1 mg/dL) align closely with those reported by Mishra (165.7, 215.0 and 225.3 mg/dL). Ghosh and colleagues similarly documented significant relationships between rising TSH and elevated total cholesterol, triglycerides, LDL and VLDL with reciprocally reduced HDL, and Marwaha and colleagues demonstrated dyslipidaemia in subclinical hypothyroidism in a large Indian population.

The finding of greatest clinical consequence concerns the intermediate stratum. Patients with a TSH above 10 mIU/L but a normal free thyroxine — biochemically subclinical by definition — already exhibited a 57.1% prevalence of grade I diastolic dysfunction, a 28.6% prevalence of septal thickening and mean total cholesterol and triglyceride concentrations exceeding NCEP ATP III desirable thresholds. In several respects these patients resembled those with overt disease more than they resembled patients with grade 1 subclinical hypothyroidism; indeed, no lipid parameter differed significantly between the grade 2 subclinical and overt strata. This pattern provides tissue-level corroboration for the epidemiological observation of Rodondi and colleagues, whose individual participant meta-analysis localised the excess risk of coronary heart disease events and mortality in subclinical hypothyroidism specifically to those with TSH concentrations of 10 mIU/L or above, and it supports the guideline position that this threshold should prompt consideration of levothyroxine replacement.

Taken together, our findings suggest that the conventional dichotomy between subclinical and overt hypothyroidism is a poor guide to cardiovascular risk, and that the degree of thyrotropin elevation is the more informative axis. From a practical standpoint, the data support obtaining an electrocardiogram and a fasting lipid profile in all patients with newly detected hypothyroidism, and considering echocardiography in those whose TSH exceeds 10 mIU/L, regardless of free thyroxine status or the presence of cardiac symptoms. Because the cardiac abnormalities of hypothyroidism are substantially reversible with adequate replacement, their detection is not merely of prognostic interest but is potentially actionable.

4.1 Strengths and limitations

Several limitations merit emphasis. First, and most importantly, the study did not include a euthyroid control group. All comparisons are therefore internal — between strata of hypothyroid severity — and the study cannot quantify the absolute excess

prevalence of any abnormality attributable to hypothyroidism relative to the background population. Statements about lipid or cardiac abnormality should be read as describing a gradient within hypothyroidism rather than a difference from normality.

Second, the cross-sectional design precludes causal inference and provides no information on reversibility; no patient was restudied after achieving euthyroidism, so the extent to which the observed abnormalities would regress with levothyroxine replacement cannot be determined from these data.

Third, the two upper strata each contained only 14 patients. The study was consequently underpowered for comparisons confined to these groups, which is the most probable explanation for the marginal p values obtained for LDL and VLDL cholesterol despite effect sizes of moderate magnitude and directionally consistent trends. These findings should be regarded as hypothesis-generating.

Fourth, diastolic function was assessed using the Canadian Consensus criteria, which were current when the protocol was designed but have since been superseded by the 2016 American Society of Echocardiography and European Association of Cardiovascular Imaging algorithm incorporating tissue Doppler e′ velocities, E/e′ ratio, left atrial volume index and tricuspid regurgitation velocity. Similarly, systolic function was evaluated by systolic time intervals rather than by biplane ejection fraction or global longitudinal strain, and the reported 2% prevalence of systolic dysfunction may therefore underestimate subtle contractile impairment.

Fifth, this was a single-centre hospital-based study of patients presenting to a tertiary care service, so referral and ascertainment bias cannot be excluded and the findings may not be generalisable to community-detected hypothyroidism. Finally, thyroid autoantibody status was not measured, and anti-thyroid peroxidase positivity has itself been associated with cardiovascular risk independent of thyroid function.

5. Conclusion

Cardiovascular morbidity and atherogenic dyslipidaemia in hypothyroidism increase progressively with the degree of thyrotropin elevation and do not begin abruptly at the threshold of overt disease. In this cohort, sinus bradycardia was the commonest electrocardiographic abnormality and left ventricular diastolic dysfunction the commonest echocardiographic abnormality, and both — together with rising total cholesterol and triglycerides and falling HDL cholesterol — tracked closely with biochemical severity.

Patients with a thyrotropin concentration above 10 mIU/L carried a burden of diastolic dysfunction, septal thickening and dyslipidaemia approaching that of overt hypothyroidism despite a normal free thyroxine, while remaining largely free of cardiac symptoms. Cardiovascular evaluation in hypothyroidism should therefore be guided by the magnitude of thyrotropin elevation rather than by the presence of symptoms or by the subclinical–overt dichotomy alone. Prospective studies with euthyroid controls and post-treatment reassessment are required to establish whether these abnormalities are reversible and whether their detection should influence the threshold for initiating replacement therapy.

Declarations

Ethics approval and consent to participate: The study protocol was approved by the Institutional Ethics Committee of Sapthagiri Institute of Medical Sciences and Research Centre (approval reference: [insert number and date]). Written informed consent was obtained from all participants.

Consent for publication: Not applicable; no individually identifiable data are presented.

Availability of data and materials: The de-identified dataset analysed during the current study is available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Figure legends

Figure 1. Frequency of presenting symptoms among 100 patients with newly detected hypothyroidism. Cardiovascular symptoms (shaded) were reported by a minority of patients despite objective electrocardiographic abnormality in 31% and echocardiographic abnormality in 24% of the cohort.

Figure 2. Prevalence of electrocardiographic abnormalities across thyroid functional strata. Bar labels indicate absolute patient numbers. All three abnormalities increased monotonically with biochemical severity; ST–T changes and low-voltage complexes were absent below a TSH of 10 mIU/L.

Figure 3. Prevalence of echocardiographic abnormalities across thyroid functional strata. Bar labels indicate absolute patient numbers. Patients with grade 2 subclinical hypothyroidism, who by definition had a normal free thyroxine, already showed a 57.1% prevalence of grade I diastolic dysfunction.

Figure 4. Fasting lipid parameters across thyroid functional strata. Bars show mean values with standard deviation whiskers; dashed lines mark NCEP ATP III desirable thresholds. Total cholesterol and triglycerides rose significantly across strata while HDL cholesterol fell.

All figures were prepared at 300 dpi and are supplied as separate image files for production.